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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/567,114	02/03/2006	Valery Khazhmuratovich Zhilov	1004398.001US (4874-7000)	2900

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EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
01/05/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

ptopatentcommunication@lockelord.com

Office Action Summary	Application No.	Applicant(s)	
	10/567,114	ZHILOV ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71,82-92 and 97-110* is/are pending in the application.

4a) Of the above claim(s) *105,107 and 109* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *71,82-92,97-104,106,108 and 110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to Applicant's Amendment and Remarks, filed 27 Oct 2010, in which claims 71, 82, 84-92 and 97-102 are amended to change the scope and breadth of the claim and claims 93-96 are canceled.

This application is the national stage entry of PCT/RU03/00346, filed 04 Aug 2003.

Claims 71, 82-92 and 97-110 are pending in the current application. Claims 105, 107 and 109, drawn to non-elected inventions, are withdrawn. Claims 103 and 71, 82-92, 97-102, 104, 106, 108 and 110 (in part) are examined on the merits herein.

Objections Withdrawn

Applicant's Amendment, filed 27 Oct 2010, with respect to objections to claims 71, 85, 86, 88-90, 93, 95, 97 and 99-101 over minor informalities has been fully considered and is persuasive, as claims 93 and 95 are canceled and amended claims 71, 85, 86, 88-90, 97 and 99-101 do not recite the identified informalities.

This objection has been **withdrawn**.

Rejections Withdrawn

Applicant's Amendment, filed 27 Oct 2010, with respect to claims 71, 81-104, 106, 108 and 110 rejected under 35 U.S.C. 112, first paragraph as not being enabling

for the full scope of diseases treated by the claimed method has been fully considered and is persuasive, as amended claims 71, 82, 84-92 and 97-102 recite treating a specific symptom or mechanism for which working examples are provided in the specification.

This rejection has been **withdrawn**.

Applicant's Amendment, filed 27 Oct 2010, with respect to claims 71, 81-104, 106, 108 and 110 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite has been fully considered and is persuasive, as claims 93-96 are canceled and amended claims 71, 86, 90, 93, 95, 97, 99 and 101 clearly recite the scope of what compounds are encompassed within the instantly claimed methods.

This rejection has been **withdrawn**.

Applicant's Amendment, filed 27 Oct 2010, with respect to claims 71, 82, 86, 88, 90, 95-98, 101-104, 106, 108 and 110 are rejected under 35 U.S.C. 102(b) as being anticipated by Minin et al. (US Patent 5,512,573, issued 30 Apr 1996, of record) has been fully considered and is persuasive, as claims 95 and 96 are canceled and amended claims 71, 82, 84-92 and 97-102 recite treatment of a patient population exhibiting the recited symptom or mechanism.

This rejection has been **withdrawn**.

Applicant's Amendment, filed 27 Oct 2010, with respect to claims 71, 82, 85, 86, 90, 93, 94-96, 99, 103, 104, 106, 108 and 110 are rejected under 35 U.S.C. 102(e) as being anticipated by Henry et al. (US Patent 6,953,799, filed 30 Oct 2002, of record) has been fully considered and is persuasive, as claims 93-96 are canceled and amended claims 71, 82, 84-92 and 97-102 recite treatment of a patient population exhibiting the recited symptom or mechanism.

This rejection under 35 U.S.C. 102(e) has been **withdrawn**.

The following grounds of rejection are reiterated.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended Claims 82, 84, 85, 87, 89, 91, 92, 98, 100 and 102 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection.

The claims recite specific diseases that are not described in the specification such a way as to reasonably convey to one skilled in the relevant art that the

inventor(s), at the time the application was filed, had possession of the now claimed invention as summarized by claim:

- 82. chronic pneumonia, pleurisy, obstructive bronchitis, anemias, pancreatic, febrile state, and rheumatoid arthritis.
- 84. radiation sickness.
- 85. insulin resistance, hyperglycemia, hyper fatty acidemia, and hyperinsulinemia.
- 87. bronchial asthma.
- 89. ischemic diseases of human brain.
- 91. chronic diffuse glomerulonephritis, sepsis, and cystic fibrosis.
- 92. tuberculosis.
- 98. cholelithiasis, inherited hemoglobinopathy, erythrocyte membranepathy, trombophlebiti, thrombosis, thrombocytosis, thrombocytopenia, cerebral blood flow abnormalities, instable angina, myocardial infarction, child's neural disorder, ischemic stroke, and migraine.
- 100. alcoholic intoxication, drug intoxication, persistent vomiting, hepatitis, hepatocirrhosis, infiltrative liver injury, hepatocellular carcinoma, cholestasis icluding pregnants, bile-duct obstruction, cholangitis, nutmeg liver, and cardiac cirrhosis.
- 102. cerebral blood flow abnormalities, embolism after surgery with vessel, ischemic stroke, and migraine.

Support for the antiacidotic effect of dimephosphon associated with regulating pneumonia is found at page 3, paragraph 34 of the instant PGPub, however no support is found for the subgenus of chronic pneumonia. Support for circulatory and tissue hypoxia, fever and peritonitis is found at page 1, paragraph 9. Support for treatment of myocardial ischemia, or ischemic diseases of the heart, caused by endocellular acidosis is found at page 2, paragraph 26. Support for treatment of thymus involution is found at page 22, paragraph 257. Support for the symptom of vomiting is found at page 1, paragraph 12, however no support is found for the subgenus of persistent vomiting. No support is found for treatment of thrombosis, however the specification spanning page 15, paragraph 182 through page 17 paragraph 207 suggest the compounds do not influence the pathological effect on a normally functioning hemostasis system, having no effect on PATT (page 16, paragraph 191), prothrombin time index (page 17, paragraph 197) or autocoagulation activity (page 17, paragraph 203).

While certain specific diseases appear in the amended claims filed 23 Mar 2009, for example at claim 73, upon further review of the specification at the time the application was filed these diseases are not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention.

Response to Applicant's Remarks:

Applicant's Remarks, filed 27 Oct 2010, have been fully considered and not found to be persuasive.

Applicant notes that the specification need not disclose and preferably omits that which is well known to those skilled in the art and available to the public. However, while the specification discloses the genus of treatment population of, for example, subjects in need of treatment of reversible abnormal changes in pH of nucleated and non-nucleated cells, the specification does not disclose the specific subgenus of patient populations wherein said reversible abnormal changes in pH are caused by chronic pneumonia (instant claim 82) or radiation sickness (instant claim 84). The specific subgenus of patient population treated is a narrowing limitation that is not supported by the as-filed disclosure because the disclosure of the genus of patient population treated would not "reasonably lead" those skilled in the art to any particular species or subgenus of patient population. See also MPEP 2163.05 II.

The following are new or modified grounds of rejection necessitated by Applicant's Amendment, filed 27 Oct 2010, in which claims 71, 82, 84-92 and 97-102 are amended to change the scope and breadth of the claim and claims 93-96 are canceled.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended Claims 71, 82, 85, 86, 90, 93, 94-96, 99, 103, 104, 106, 108 and 110 are rejected under 35 U.S.C. 103(a) as being unpatentable over Henry et al. (US Patent 6,953,799, filed 30 Oct 2002, of record).

Henry et al. discloses phthalazine compounds such as 5-amino-2,3-dihydro-1,4-phthalazinedione, also known as luminol, (column 1, lines 45-50) administered to treat hosts with diseases involving impaired or aberrant intracellular redox states, which affects the membrane proton gradient, resulting in intracellular acidosis, and causes oxygen deficiency in cells and excessive formation of the free radical superoxide (column 2, lines 40-55). Henry et al. discloses said phthalazine compounds incorporated into pharmaceutical forms (column 2, lines 65-70 and column 3, lines 1-5), and discloses the sodium form of a phthalazine compound (column 17, lines 50-55), leading one of skill in the art to instantly envision the well-known pharmaceutically acceptable sodium salt. Henry et al. teaches this therapy for treating, for example, atherosclerosis, burns, and chronic viral infections of the liver (column 4, lines 35-50), a

hepatoprotective therapy. Henry et al. discloses it is known that said compound has an effect to treat the nitrergic mechanisms of cells in the central nervous system (column 10, lines 10-45). Henry et al. discloses said compound to treat insulin resistance, hyperglycemia, hyper fatty acidemia, hyperinsulemia, rheumatoid arthritis and amyotrophic lateral sclerosis (claim 1 at column 18, lines 20-30). These diseases are necessarily caused by chemical compounds action, such the action of chemical compounds in the deficiency of oxygen or the action of oxygen radicals.

Henry et al. does not specifically disclose the method of treatment of subjects in need of treatment of reversible abnormal changes in pH of nucleated and non-nucleated cells in order to normalize the endocellular pH to the physiologically acceptable levels (instant claim 71). Henry et al. does not specifically disclose the method of treatment of subjects in need of treatment of oxygen deficiency in nucleated and non-nucleated cells (instant claim 86). Henry et al. does not specifically disclose the method of treatment of subjects in need of treatment of excessively-formed free radicals in nucleated and non-nucleated cells (instant claim 90). Henry et al. does not specifically disclose the method of treatment of subjects in need of hepatoprotection (instant claim 99).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teaching of Henry et al. in order to treat the recited mechanism of action in a subject in need of such treatment. One of ordinary skill in the art would have been motivated to combine the teaching of Henry et al. in order to treat said mechanism in said subjects with a reasonable expectation of success because Henry et al. discloses the administration to treat hosts with diseases involving impaired or

aberrant intracellular redox states, which affects the membrane proton gradient, resulting in intracellular acidosis, and causes oxygen deficiency in cells and excessive formation of the free radical superoxide. It would have been routine experimentation to administer the compound in order to treat the membrane proton gradient, resulting in intracellular acidosis, oxygen deficiency in cells and excessive formation of the free radical superoxide because Henry et al. discloses this to be the mechanism by which the treated conditions occur.

Response to Applicant's Remarks:

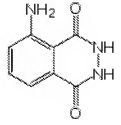
Applicant's Remarks, filed 27 Oct 2010, have been fully considered and not found to be persuasive.

As recited above, Applicant is persuasive that Henry et al. does specifically disclose explicitly or inherently treating a patient in need of the treatments recited in the instant claims. However, while Applicant notes that Harry discloses embodiments of a method of regulating thiol or oxygen redox states, the broader teaching of Harry is that diseases involving impaired or aberrant intracellular redox states, which affects the membrane proton gradient, resulting in intracellular acidosis, and causes oxygen deficiency in cells and excessive formation of the free radical superoxide (column 2, lines 40-55). Affecting the membrane proton gradient would obviously result an abnormal change in pH based what one of ordinary skill in the art would have understood regarding the role of the concentration of H^+, or pH, in defining the membrane proton gradient. Therefore it would have been obvious to one of ordinary skill in the art at the time of the invention to treat subjects in need of such treatment

based on guidance provided by the broader teaching of Harry that the diseases involve impaired or aberrant intracellular redox states, which affects the membrane proton gradient. Further, instant claim 71 recites "in order to normalize the endocellular pH to the physiologically acceptable levels." It would be obvious to one of ordinary skill in the art that any living cell would have an endocellular pH at physiologically acceptable levels, because physiologically unacceptable levels would result in cell ceasing to function.

Applicant remarks that disruption of the proton gradient would not necessarily result in pH changed to an abnormal level. However, instant claim 71 is drawn to "reversible abnormal changes in pH of nucleated and non-nucleated cells", and does not specify level to which the pH is changed. A change in the concentration of H^+ defining the membrane proton gradient that is perturbed by oxidant stresses would be a reversible abnormal change in pH because pH is a function of H^+ concentration and a perturbation by oxidant stresses causes a reversible abnormal change. The instant claims do not require a magnitude by which the pH is changed, therefore encompasses any reversible abnormal change in pH.

Claims 71, 82, 86, 88, 90, 97, 98, 101-104, 106, 108 and 110 are rejected under 35 U.S.C. 103(a) as being unpatentable over Minin et al. (US Patent 5,512,573, issued 30 Apr 1996, of record) in view of Henry et al. (US Patent 6,953,799, filed 30 Oct 2002, of record).

Minin et al. discloses the use of 5-aminophthaloylhydrazide and its salts administered in effective amounts as anti-hypoxic and defensive agents (abstract). The compound 5-aminophthaloylhydrazide or Luminol (column 1, lines 20-25), has the chemical structure  corresponding to the elected species. Minin et al. discloses the use of the sodium salt of 5-aminophthaloylhydrazide (column 4, lines 30-35). Minin et al. discloses the administration for the therapeutic effect of antioxidant action to treat acute hypoxia of myocardial infarct or heart attack (column 4, lines 50-55 and column 7, lines 45-50), a form of arterial hypoxia and an ischemic disease of the heart. Minin et al. discloses the administration for treatment of an excess of free oxygen radicals (column 4, line 60). Minin et al. discloses the administration for the therapeutic effect of acute alterations in the blood stream to the brain (column 8, lines 45-55), or cerebral blood flow abnormalities.

Minin et al. does not specifically disclose the method of treatment of subjects in need of treatment of reversible abnormal changes in pH of nucleated and non-nucleated cells in order to normalize the endocellular pH to the physiologically acceptable levels (instant claim 71). Minin et al. does not specifically disclose the method of treatment of subjects in need of treatment of oxygen deficiency in nucleated and non-nucleated cells (instant claim 86). Henry et al. does not specifically disclose the method of treatment of subjects in need of treatment of excessively-formed free radicals in nucleated and non-

nucleated cells (instant claim 90). Minin et al. does not specifically disclose the method of treatment of subjects in need of treatment of increased aggregation of thrombocytes and erythrocytes (instant claim 97). Minin et al. does not specifically disclose the method of treatment of subjects in need of prophylaxis of decreasing the aggregation of thrombocytes and erythrocytes (instant claim 101).

It is well known to one of ordinary skill in the art that myocardial infarct is commonly due to formation of a blood clot or aggregation of thrombocytes.

Henry et al. teaches phthalazine compounds such as 5-amino-2,3-dihydro-1,4-phthalazinedione, also known as luminol, (column 1, lines 45-50) administered to treat hosts with diseases involving impaired or aberrant intracellular redox states, which affects the membrane proton gradient, resulting in intracellular acidosis, and causes oxygen deficiency in cells and excessive formation of the free radical superoxide (column 2, lines 40-55). Henry et al. teaches while said phthalazine compounds are described as anti-hypoxic agents for use in treating specific disorders their role in modulating intracellular redox status and cell fates was not recognized (spanning column 1, lines 60-65 and column 2, lines 1-5).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Minin et al. in view of Henry et al. One of ordinary skill in the art would have been motivated to combine Minin et al. in view of Henry et al. because both Minin et al. and Henry et al. teach administration of phthalazine compounds such as 5-amino-2,3-dihydro-1,4-phthalazinedione, also known as luminol to treat oxygen deficiency in cells and excessive formation of the free radical superoxide, suggesting

administering to patients in need of such treatment. One of ordinary skill in the art would have had a reasonable expectation of success to combine Minin et al. in view of Henry et al. because the mechanism of action of the treatment of Minin et al. is taught by Henry et al. to be merely not recognized and Henry et al. suggests a mechanism of action of luminol. It would have been obvious to one of ordinary skill in the art at the time of the invention to treat subjects in need of treatment of or prophylaxis for increased aggregation of thrombocytes and erythrocytes because Minim et al. discloses the administration for the therapeutic effect of antioxidant action to treat acute hypoxia of myocardial infarct and it is well known to one of ordinary skill in the art that myocardial infarct is commonly due to formation of a blood clot or aggregation of thrombocytes

Response to Applicant's Remarks:

Applicant's Remarks, filed 27 Oct 2010, have been fully considered and not found to be persuasive.

As recited above, Applicant is persuasive that Minim et al. does specifically disclose explicitly or inherently treating a patient in need of the treatments recited in the instant claims.

Applicant's remarks with regard to Henry et al. are addressed as above.

Conclusion

No claim is found to be allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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